IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	F.C. Prats
Art Unit	:	1651
Applicant	:	Bruce Joseph Roser
Serial No.	:	08/875,796
Filed	:	October 30, 1998
For	:	Dried Blood Factor Compositions Comprising Trehalose

DECLARATION OF FRANCIS E. PRESTON UNDER 37 CFR 1.132

I, Francis E. Preston, hereby declare that:

My C.V. is attached.

I have read and understood the subject application, and the Office Action dated December 13, 2001. I have also reviewed the following references:

Curtis *et al.* (U.S. Patent No. 5,576,291, issued November 19, 1996)

Livesey *et al.* (U.S. Patent No. 5,364,756, issued November 15, 1994)

AND, being thus duly qualified, do further declare:

Factor VIII is a critical component in the human blood clotting process. Factor VIII deficiencies are responsible for haemophilia A which is a blood clotting disease afflicting a significant number of people. Through the administration of Factor VIII to those with haemophilia A, it is possible to minimize disability and to prolong life.

Unfortunately, obtaining sufficient quantities of Factor VIII to meet the demand for treating haemophilia patients has been very difficult. Factor VIII is present in low concentrations in blood plasma making it difficult to purify large quantities of Factor VIII. Also, plasma-derived blood factors carry a risk of transmitting viruses and other infectious agents.

Although the gene which encodes Factor VIII was identified in the mid-1980's, technical problems have hindered the ability to produce sufficient quantities of therapeutic preparations of

recombinant Factor VIII. One of the primary technical challenges is to stabilize the highly labile Factor VIII. Factor VIII is an extremely delicate protein, regardless of whether it is produced recombinantly or purified from plasma. Native Factor VIII contains multiple enzymatic cleavage sites making it highly susceptible to degradation. In the past, degradation of Factor VIII preparations has been avoided or minimized using albumin as a stabilizing agent.

Factor VIII purified from plasma necessarily contains albumin. Although the presence of albumin increases the chances for contamination with pathogens, albumin has been left in Factor VIII compositions purified from plasma because albumin was believed to be necessary to stabilize Factor VIII. Furthermore, until recently, a stabilizing amount of albumin was actually added to all therapeutic recombinant Factor VIII preparations. This practice has continued despite the potential health risks associated with albumin.

For years, it has been well known to those skilled in the art that Factor VIII, which is a large protein having over 2000 amino acids, is highly susceptible to degradation. In the human body, enzymes act on native Factor VIII during the clotting process. As the result of a complicated enzymatic conversion process, Factor VIII is transformed *in* vivo into a heterotrimer known as activated Factor VIII (Factor VIIIa). Specifically, proleolytic processing by thrombin results in the formation of Factor VIIIa which is, itself, a cofactor in the activation of Factor X by Factor IXa. Native Factor VIII is not a cofactor in the conversion of Factor X.

Thus, activated Factor VIII is a different chemical entity than Factor VIII. Activated Factor VIII has chemical, physical and physiological properties which all differ from Factor VIII. The scientific literature is replete with references to Factor VIII as well as to Factor VIIIa. The skilled artisan, in 1995, would be fully aware of the different nature of these compounds. The skilled artisan would also have been fully aware of the delicate nature of Factor VIII and the standard practice of stabilizing Factor VIII with albumin. At the time of the subject invention, those skilled in the art would recognize that "native Factor VIII" does not refer to activated Factor VIII.

Unlike Factor VIII, activated Factor VIII is not produced recombinantly. Rather, activated Factor VIII is produced by subjecting Factor VIII to proteolytic cleavage. This can be done, for example, by the process described by Curtis *et al.*

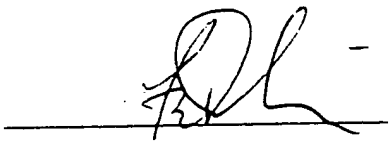
The Curtis *et al.* patent pertains to the administration of activated Factor VIII to treat a

particular complication of haemophilia. Curtis *et al.* intentionally proteolytically cleaves Factor VIII to obtain activated Factor VIII. This, of course, does not provide the skilled artisan with any information regarding the stability of Factor VIII, since the Factor VIII was purposefully degraded. I have not identified any disclosure in the Curtis *et al.* reference which would teach or suggest that native Factor VIII can be stabilized by trehalose in the absence of added albumin.

Finally, from my review of the Livesey *et al.* patent I again find no disclosure which would teach or suggest to a person skilled in this art that highly labile Factor VIII could be stabilized by trehalose in the absence of added albumin.

The undersigned declares further that all statements made herein of his own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Application or any Patent issuing thereon.

Further declarant sayeth naught

Signed: 

Date: 24.5.02

CURRICULUM VITAE

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FEP/SLR
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